Original Article

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ADVERSE METABOLIC EFFECTS OF CONVENTIONAL AND ATYPICAL ANTIPSYCHOTICS: A COMPARATIVE STUDY

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ABSTRACT

Objective: To compare the adverse metabolic effects (changes in Body Mass Index, fasting blood glucose and serum cholesterol levels) of conventional and atypical antipsychotics in patients of psychosis.

Study Design: Randomized Control Trials (RCT).

Place and Duration of Study: Department of Psychiatry, Military Hospital Rawalpindi from August 2007 to August 2008.

Patients and Methods: A total of 110 patients were assigned to treatment with haloperidol (n=35), risperidone (n=36) and olanzapine (n=39). Fasting blood glucose, serum cholesterol levels and BMI were computed at baseline and subsequently repeated at 2nd week, 6th week and 8th week of treatment. In all the subjects, all the blood samples were drawn as a fasting sample in early morning.

Results: ANOVA analyses indicated that changes in mean fasting glucose and cholesterol levels reached significance in period 2 (from 2nd week to 6th week) but not in period 1 (from 0 to 2nd week) and period 3 (from 6th week to 8th week). The increase in mean fasting glucose and cholesterol levels over time reached statistical significance in the olanzapine group after 6 weeks. No significant change in glucose was detected in the haloperidol and risperidone groups. The largest weight gain was seen with olanzapine (mean=2.4 Kg), followed by risperidone (mean=1.25 Kg). There was minimal weight gain with haloperidol (mean=0.3 Kg).

Conclusion: There was a higher risk of adverse metabolic effects with olanzapine treatment as compared to risperidone and haloperidol in the study population. The metabolic effects appear between 2 to 6 weeks after starting treatment.

Keywords: Atypical antipsychotics, Body Mass Index, Metabolic changes.

INTRODUCTION

Abnormalities in glucose regulation have been reported in schizophrenia before and after the introduction of antipsychotic medications. Hyperglycemia in the context of treatment with atypical antipsychotic medications has been documented in several series of case reports, and olanzapine has been implicated more frequently than risperidone. Complicating this issue is the observation that patients with schizophrenia are more likely to develop diabetes mellitus than the general population, regardless of antipsychotic use.

Large epidemiological studies have provided conflicting information regarding the relative risk of diabetes and exposure to different antipsychotics[1]. Case reports have linked treatment with clozapine and olanzapine to hyperlipidemia that disappears when antipsychotic medications are discontinued[2-4]. Medical record reviews further support a connection between clozapine and olanzapine and the increased risk of hypertriglyceridemia[5,6]. In one case-control study, olanzapine and clozapine, but not risperidone or combination therapy, were associated with a significantly increased risk of hyperlipidemia[7].

Clinical epidemiological studies provide a second line of evidence linking treatment with antipsychotic medications to an increased risk of hyperlipidemia[7,8]. Prospective research further suggests that antipsychotic medications may adversely affect serum lipids. In one randomized double-blind controlled trial, olanzapine and clozapine resulted in significant increases in total serum cholesterol[9]. In a 4-week trial, olanzapine and risperidone in

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combination with divalproex were associated with statistically nonsignificant increases in total serum cholesterol[10]. However, the true incidence of both hyperglycemia and hypercholesterolemia induced by different typical or atypical medications is not known in Pakistan at this time.

PATIENTS AND METHODS

It was an interventional comparative study, which was carried out at Department of Psychiatry, Military Hospital Rawalpindi. A total of 110 patients were assigned to treatment with haloperidol (n=35), risperidone (n=36) and olanzapine (n=39).

Patients diagnosed with psychosis reporting to the facility and consenting for participation in the study were randomly assigned to the three groups of antipsychotics using random number table.

Indoor patients and their next of kin consenting to participate for 8 weeks of indoor treatment with antipsychotics were included in the study. Patients with history of failure to respond to risperidone, history of olanzapine, risperidone, or haloperidol intolerance, depot antipsychotic treatment within 30 days before random assignment to one of the three drugs and substantial medical illness were excluded from the study.

Patients and their next of kin were told about the nature and purpose of the study and their consent was obtained. The sample was drawn from the patients reporting to the tertiary care mental health facility of Military Hospital Rawalpindi.

A total number of 110 patients diagnosed with psychosis according to the ICD-10 criteria were taken as the sample and were randomly split into the 3 groups. Those patients who were on antipsychotics were admitted and taken off the medication and a 'wash-out' period of 72 hours was observed. An initial early morning, fasting blood sample was obtained for the measurement of fasting blood glucose and serum cholesterol levels prior to the administration of antipsychotic medication – conventional (Haloperidol) and atypical (Risperidone and Olanzapine). Height and weight was also measured to calculate the BMI. These were recorded as "baseline levels".

Doses of the antipsychotic medications were adjusted according to the clinical assessment of the patients' mental state.

Fasting blood sugar, serum cholesterol levels and weight were repeated at 2nd, 6th and 8th week of treatment.

The patients in the study were aware of the medication they were receiving and thus were not blinded. Those doing the measurements were not blinded as well. The variables involved in the study were

- Age
- Gender
- Body Mass Index
- Blood Glucose Fasting
- Serum Cholesterol

Data Analysis

All analyses were carried out through Statistical Package for Social Sciences (SPSS) 13.

Study variables were compared by using Analysis of ariance (ANOVA), following by post-hoctukey teast. P-values<0.05 was considered as significant.

RESULTS

Age abd gender description f all the groups are given in table-1 and 2. All the groups were compareable with respect to age (p>0.05) and gender (p>0.05).

Differences among treatment groups reached significance in period 2 (from 2nd to 6th week) but not in period 1 (from 0 to 2nd week) and period 3 (from 6th to 8th week).

Differences among treatment groups of cholistrol reached significance after 6 weeks.

The largest weight gain was seen with olanzapine, followed by risperidone. There was minimal weight gain with haloperidol.

DISCUSSION

Our study shows that olanzapine is associated with significantly elevated mean

Table 1: Mean Ages of the Study Groups

Medication	Mean Age	Standard Deviation
Haloperidol (N=35)	33.77	10.34
Risperidone (N=36)	35.11	9.94
Olanzapine (N=39)	37.28	10.31

Table 2: Gender Distribution of the Study Groups

Gender	Antipsychotic Used		
	Haloperidol N=35	Risperidone N=36	Olanzapine N=39
Male	23 (65.7%)	24 (66.7%)	26 (66.7%)
Female	12 (34.3%)	12 (33.3%)	13 (33.3%)

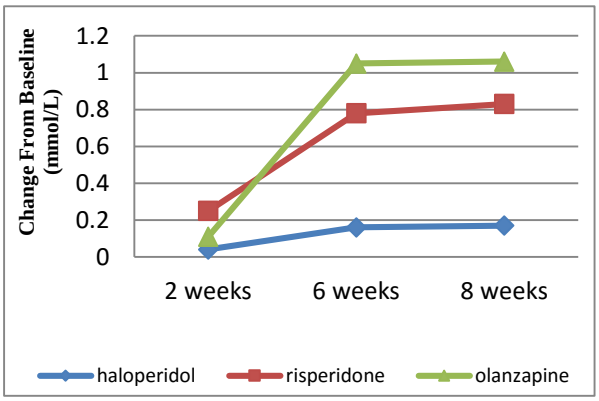

Figure 1: Change in Mean Glucose from Baseline over Time.

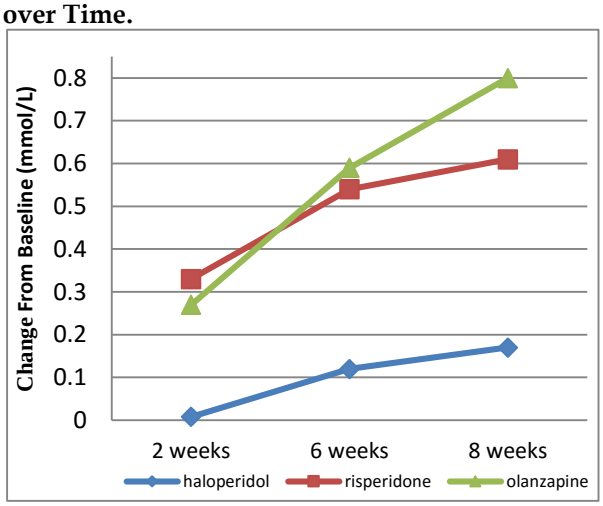

Figure 2: Change in Mean Cholesterol from Baseline over Time.

glucose levels after 6 weeks of treatment and that risperidone and haloperidol were not associated with significant increases. The mean increases were modest and remained within clinically normal ranges, but 6.3% of patients (six given olanzapine and one given risperidone) developed abnormally high glucose levels (>6.1 mmol/l) during the course of their treatment. Changes in glucose levels were independent of weight increase in all three treatment groups, despite significant weight gains, which were highest for olanzapine, followed by risperidone.

In a nonrandomized study that compared the atypical and typical antipsychotics as our study, similar results were found for olanzapine[11]. When challenged with a modified glucose tolerance test, the olanzapine-treated group had significant elevations in post load

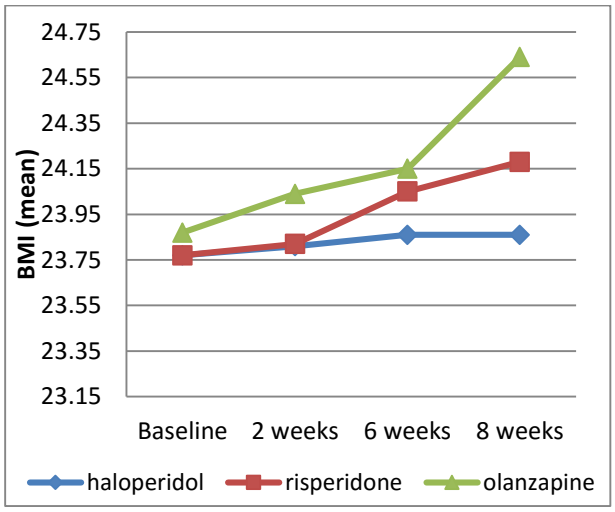

Fig. 3: Change in Mean BMI over Time

glucose levels at all time points compared with untreated control subjects and haloperidol-treated patients.

Among the traditional neuroleptics, chlorpromazine[12] and thioridazine[13] are the agents most closely associated with diabetes mellitus, although the associations are weaker than those with olanzapine or clozapine. In our study, the typical antipsychotic haloperidol was associated with an elevation of mean glucose levels within a clinically normal range. Haloperidol has been reported to increase insulin resistance and to be associated with higher fasting glucose levels in obese women compared with control subjects[14]. Haloperidol has also been reported to be associated with higher glucose levels in schizophrenia subjects than control subjects during the glucose tolerance test[15]. Increased insulin resistance in peripheral tissues can be caused by

hyperprolactinemia[16] and may be involved in the mechanism underlying hyperglycemia in patients treated with typical antipsychotics.

The second important finding of our study was that increase in mean cholesterol levels over time reached statistical significance in the olanzapine group after 6 weeks. There was no significant elevation in cholesterol levels with risperidone and haloperidol. A similar association between elevated cholesterol and olanzapine treatment was reported by Kinon et al.[17] Our findings are consistent with open-label and retrospective data demonstrating a greater association of olanzapine treatment than risperidone treatment with increases in cholesterol[18]. Henderson et al. found significant increases in both fasting cholesterol and triglycerides in a group of 81 patients treated with clozapine[19]. It appears that the more pronounced effect of antipsychotic treatments on lipid metabolism may be on triglycerides[20], which were not measured in the present study.

In our study, the largest weight gain was seen with olanzapine followed by risperidone. There was minimal weight gain with haloperidol. A similar association between weight gain and olanzapine treatment was reported by Kinon et al[17].

CONCLUSIONS

Risk of development of hyperglycemia, hypercholesterolemia is significantly high in patients treated with olanzapine.

Olanzapine treatment is associated with higher weight gain as compared to risperidone and haloperidol at the end of 8 weeks of treatment.

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